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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,362	07/23/2003	Pei Kan	38847-191328	7671
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VENABLE LLP P.O. BOX 34385 WASHINGTON, DC 20043-9998			EXAMINER SCHLIENTZ, NATHAN W	
			ART UNIT 1616	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/624,362	Applicant(s) KAN ET AL.	
	Examiner Nathan W. Schlientz	Art Unit 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>7/2/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7 June 2007 has been entered.

Status of Claims

Claims 1, 12, 15, 18-19, 21, 30, 33, 36-37 have been amended and claims 39-44 have been newly added in an Amendment filed 7 June 2007. As a result, claims 1-44 are pending and are examined herein on the merits for patentability. No claim is allowed at this time.

Response to Amendment

1. The amendment filed 4 December 2006 stands objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: docetaxel, retinol, retinyl acylate, retinyl acetate, the multiple derivatives of

camptothecin, polyethylene glycol 600 mono(cholesteryl)ether sebecate and cholesteryl oleyl carbonate.

Applicants have amended the Specification paragraphs [0026], [0050], [0051], [0054], and [0055] to include the derivatives of paclitaxel, retinoic acid, camptothecin, and cholesterol. The Applicants also state that the derivatives of paclitaxel, retinoic acid, camptothecin, and cholesterol have been limited to well-known compounds (Remarks filed 4 December 2006, page 21, lines 10-21). However, the specification as originally filed does not provide support for the derivatives listed in the presently amended claims.

Applicant is required to cancel the new matter in the reply to this Office Action.

Withdrawn Rejections/Objections

1. The objection to the amendment to the specification filed 4 December 2006 with respect to the amendment of paragraph [0043] is hereby withdrawn by the examiner in light of the cancellation of the recitation of the molar ratio of the first phospholipid to the second phospholipid is larger than 1/20.
2. The rejection of claims 12-19 and 30-37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn by the examiner in light of the aforementioned amendments to claims 12, 15, 18-19, 30, 33 and 36-37, wherein applicant's have limited the derivatives to select compounds.

3. The rejection of claims 12-18 and 30-36 under 35 U.S.C. 112, first paragraph, is hereby withdrawn by the examiner in light of claim amendments.
4. The remainder of the rejections from the Official Action mailed 7 March 2007 are maintained and new rejections are added.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 8-12, 15, 18-19, 26-30, 33 and 36-37 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The recitation of docetaxel (Claims 8-11, 18, 26-29 and 36); retinol, retinyl acylate and retinyl acetate (Claims 12, 18, 30 and 36); the multiple derivatives of camptothecin (Claims 15, 18, 33 and 36); and polyethylene glycol 600 mono(cholesteryl)ether sebecate and cholesteryl oleyl carbonate (Claims 19 and 37) are not supported by the original disclosure and are therefore considered new matter. The claims are therefore indefinite for being drawn to material that is considered new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-9 and 18-19 stand rejected while claims 39-40 are newly rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,415,869 (hereinafter Straubinger et al.).

Straubinger et al. disclose a pharmaceutical formulation comprising at least one taxane present in a pharmaceutically effective amount of 1.5-8 mol% and a mixture of one or more negatively charged phospholipids and one or more zwitterion phospholipids in a respective ratio of 1:9 to 3:7 (claim 1). Also, Straubinger et al. disclose the negatively charged phospholipids include dipalmitoylphosphatidyl glycerol, distearyl glycerol, and dipalmitoylphosphatidyl serine (claim 2), and the zwitterion phospholipids include dioleoylphosphatidyl choline and dilauroylphosphatidyl choline (claim 3). Straubinger et al. further disclose the pharmaceutical formulation wherein the taxane is taxol (paclitaxel, see claim 6) and further comprising cholesterol (see claim 8). Therefore, Straubinger et al. fully anticipate all the limitations of the instant claims.

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2. Claims 1-7, 19, 21-25 and 37 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,873,089 (hereinafter Scotto et al.).

Scotto et al. disclose a proteoliposome formulation comprising a lipid component/phospholipid, i.e. egg or soy phosphatidylcholine (EPC or SPC) and a fusogen, i.e. distearoyl phosphatidylcholine, dipalmitoylphosphatidyl choline, hydrogenated egg phosphatidylcholine or hydrogenated soy phosphatidylcholine (HEPC or HSPC) (see column 5, lines 37-64; and Claims 1, 5 and 6), wherein the amount fusogen is greater than 0 but less than 80 mol%, preferably 1-10 mol% in relation to bulk phospholipid of the bilayer (column 6, lines 4-7). Scotto et al. further disclose the fusogen to be any lipophilic molecule (column 5, lines 14-18). Thus, the fusogens disclosed by Scotto et al. are inherently hydrophobic substances. Scotto et al. further disclose the proteoliposomes comprising a saturated fatty acid, optionally cholesterol, as well as a 9/21 ratio (i.e. about 6.9/16) of fusogen to phospholipid (see example 3; and column 10, lines 24-45). Scotto et al. also disclose the association of the said formulation with a drug (see column 8, lines 11-37). Therefore, Scotto et al. fully anticipate all the limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Straubinger et al. in view of U.S. Patent 5,424,073 (hereinafter Rahman et al.).

Applicant claims:

Applicants claim a liposome according to claim 1, wherein at least 20 mole% of the hydrophobic substance is incorporated in the liposome and the liposome remains at at least about 70% of incorporation efficiency at the sixth month.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Straubinger et al. teach liposomal formulations comprising at least one taxane present in a pharmaceutically effective amount of 1.5-8 mol% and a mixture of one or more negatively charged phospholipids and one or more zwitterion phospholipids in a respective ratio of 1:9 to 3:7, as discussed above.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Straubinger et al. do not teach the taxane present in the liposomal formulation in an amount of at least 20 mole%. However, Rahman et al. teach liposomal formulations comprising taxol, phosphatidyl choline and/or phosphatidyl serine, and cholesterol (column 3, lines 24-54). Rahman et al. teach the liposomal formulations comprising 15-20 mol% taxol as assayed by HPLC (Examples 1-4). Rahman et al. further teach that the liposomal formulations of their invention provides a delivery system characterized by avoidance of solubility problems, improved taxol stability, ability to administer taxol as a bolus or short infusion rather than extended (24-hour) infusion of free taxol, increased therapeutic efficacy of taxol and modulation of multidrug resistance in cancer cells (column 2, lines 60-68). Rahman et al. further teach extended stability and incorporation efficiency of the liposomal formulations (column 4, line 51 through column 5, line 11).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to incorporate approximately 20 mol% taxol within the liposomal formulations of Straubinger et al. in order to avoid of solubility problems, improve taxol stability, administer taxol as a bolus or short infusion rather than extended (24-hour) infusion of free taxol, increase therapeutic efficacy of taxol and modulate multidrug resistance in cancer cells, as reasonably taught by Rahman et al. One of ordinary skill would have had an expectation of success because Rahman et al. teach liposomal formulations comprising up to 20 mol% taxol that are stable for at least 5 months and suitable for therapeutic use.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 20 and 38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Scotto et al. in view of and Crosasso et al., Journal of Controlled Release (2000) 63, 19-30 (hereinafter Crosasso et al.).

Applicant claims:

Applicants claim a liposome for incorporating high content of hydrophobic substances comprising a first phospholipid and a second phospholipid (claims 1 and 21), and the liposome-forming material MPEG-DSPE.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Scotto et al. teach liposome formulations comprising a fusogen and a phospholipid, wherein the fusogen include distearoyl phosphatidylcholine, dipalmitoylphosphatidyl choline, hydrogenated egg phosphatidyl choline or hydrogenated soy phosphatidyl choline and the phospholipids include egg or soy phosphatidylcholine. Scotto et al. further disclose the lipid vesicle associated with a drug or other biologically active or physiologically active agent, as discussed above.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Scotto et al. do not teach the addition of MPEG-DSPE with the liposome formulations. However, it is known in the art that polyethylene glycol conjugated, "PEGylated", liposomes have a longer circulation time in the bloodstream prior to being metabolized. Therefore, liposome formulations being used to carry drugs to target cells via intravenous injection benefit greatly from the addition of PEG or PEG derivatives by

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allowing lower dose injections because the amount of drug reaching the target cells would be increased. It is for that reason the examiner joins Crosasso et al.

Crosasso et al. teaches liposome preparations by employing hydrophilic polymer-conjugated phospholipid (methoxy polyethylene glycol-phosphatidylethanolamine) in order to enhance the liposomes circulation time in blood (page 20, 2nd column, lines 6-24). Crosasso et al. further teaches the incorporation of cholesterol within the "PEGylated" (polyethylene glycol conjugated) liposomes comprising EPC, phosphatidylglycerol (PG), and paclitaxel (abstract; page 23, 2nd column, lines 14-17; and Table 1).

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-43)

Accordingly, in order to prolong the circulation in the bloodstream for the formulations of Scotto et al. it would have been obvious to one skilled in the pertinent art at the time of the instant invention to combine the liposome compositions of Scotto et al. with MPEG-DSPE as in Crosasso et al. The persons skilled in the art would have had reason to expect the PEGylated liposomes comprising HEPC or HSPC and EPC or SPC, cholesterol, drug, and MPEG-DSPE would have delivered the said drug to the target cell more efficiently because of the prolonged circulation within the bloodstream.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

3. Claims 8-18 and 26-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Scotto et al. in view of U.S. Patent No. 5,733,572 (hereinafter Unger et al.) and U.S. Patent No. 5,776,486 (hereinafter Castor et al.).

Applicant claims:

Applicants claim liposome formulations comprising a first and second phospholipid as in instant claims 1 and 21, and further incorporating paclitaxel, retinoic acid or camptothecin.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Scotto et al. teach liposome formulations comprising a fusogen and a phospholipid, wherein the fusogen include distearoyl phosphatidylcholine, dipalmitoylphosphatidyl choline, hydrogenated egg phosphatidyl choline or hydrogenated soy phosphatidyl choline and the phospholipids include egg or soy phosphatidylcholine. Scotto et al. further disclose the lipid vesicle associated with a drug or other biologically active or physiologically active agent, as discussed above.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Scotto et al. do not teach the hydrophobic substances paclitaxel, retinoic acid, and camptothecin being encapsulated in their liposome formulations. It is known in the

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art that liposome-based drug formulations are able to achieve the equivalent therapeutic efficacy to free drug, as well as reduce the systemic toxicity in many applications (for example, Castor et al., column 1, lines 33-36). Because of the toxicity associated with free paclitaxel, camptothecin, and retinoic acid it would be beneficial to incorporate these drugs within the liposome formulations of Scotto et al. to reduce the toxic side effects. It is for that reason the examiner joins Unger et al. and Castor et al.

Unger et al. teach dipalmitoylphosphatidylcholine (DPPC) liposomes incorporating vitamin A (retinoic acid) (see example 8, column 53, line 6-15). Unger et al., however, doesn't teach liposome formulations comprising a first and a second phospholipid, a liposome-forming material such as cholesterol, antioxidant, or PEGylated lipids.

Castor et al. teach encapsulation of paclitaxel or camptothecin within liposomes comprising EPC and cholesterol. However, Castor et al. do not disclose the use of a first and second phospholipid chosen based upon their phase transition temperatures.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Accordingly, it would be obvious to one skilled in the pertinent art at the time of the invention to employ the liposomes of Scotto et al. in combination with any hydrophobic substance of Castor et al. and/or Unger et al., because the persons skilled in the art would have had a reasonable expectation of success in conventionally encapsulating a drug of choice (paclitaxel, retinoic acid, or camptothecin) within the

liposomes of Scotto et al. and reducing the side effects associated with the toxicity of the drugs.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

4. Claims 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scotto et al., in view of Unger et al. and Castor et al., as applied to claim 21 above, and further in view of Rahman et al.

Applicant claims:

Applicants claim a liposome according to claim 21, wherein 3-25 mol%, 8-25 mol%, or at least 20 mole% of the hydrophobic substance is incorporated in the liposome and the liposome remains at at least about 70% of incorporation efficiency for at least 60 days, preferably at the sixth month.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Scotto et al. teach liposome formulations comprising a fusogen and a phospholipid; Unger et al. teach dipalmitoylphosphatidylcholine (DPPC) liposomes incorporating vitamin A (retinoic acid); and Castor et al. teach encapsulation of

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paclitaxel or camptothecin within liposomes comprising EPC and cholesterol, as discussed above.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Scotto et al. in view of Unger et al. and Castor et al. does not teach the hydrophobic substance (paclitaxel, retinoic acid or camptothecin) present in the liposomal formulation in an amount of 3-25 mol%, 8-25 mol%, or at least 20 mole%, as instantly claimed. However, Rahman et al. teach liposomal formulations comprising taxol, phosphatidyl choline and/or phosphatidyl serine, and cholesterol (column 3, lines 24-54). Rahman et al. teach the liposomal formulations comprising 15-20 mol% taxol as assayed by HPLC (Examples 1-4). Rahman et al. further teach that the liposomal formulations of their invention provides a delivery system characterized by avoidance of solubility problems, improved taxol stability, ability to administer taxol as a bolus or short infusion rather than extended (24-hour) infusion of free taxol, increased therapeutic efficacy of taxol and modulation of multidrug resistance in cancer cells (column 2, lines 60-68). Rahman et al. further teach extended stability and incorporation efficiency of the liposomal formulations (column 4, line 51 through column 5, line 11).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to incorporate up to 20 mol% of paclitaxel, retinoic acid or camptothecin in the liposomal formulations of Scotto et al., Unger et al. and Castor et al.

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in order to avoid of solubility problems, improve taxol stability, administer taxol as a bolus or short infusion rather than extended (24-hour) infusion of free taxol, increase therapeutic efficacy of taxol and modulate multidrug resistance in cancer cells, as reasonably taught by Rahman et al. One of ordinary skill would have had an expectation of success because Rahman et al. teach liposomal formulations comprising up to 20 mol% taxol that are stable for at least 5 months and suitable for therapeutic use.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's Remarks filed 7 June 2007 have been fully considered but they are not persuasive.

1. Applicants argue on page 16 of the aforementioned Remarks that Straubinger et al. do not disclose that a molar ratio of the first to second phospholipids is no less than 3 to 16. However, the examiner respectfully disagrees. Straubinger et al. disclose the ratio of one or more negatively charged phospholipid to one or more zwitterion phospholipid is 1:9 to 3:7 (claim 1).

2. Applicants also argue on page 16 that Straubinger et al. fail to teach or suggest a liposome formulation for incorporating a high content of hydrophobic substances. However, instant claim 9 is drawn to a liposomal formulation for incorporating high content of hydrophobic substances, wherein the hydrophobic substance is paclitaxel incorporated with a drug/lipid ratio ranging from about 0.5 to 25 mol%. Straubinger et al. disclose incorporating 1.5-8.0 mol% taxane, which is within the range of 0.5 and 25 mol%. Therefore, Straubinger et al. incorporate "high content" of taxane.

3. Applicants argue on page 16 of the aforementioned Remarks that Scotto et al. do not disclose that a molar ratio of the first to second phospholipids is no less than 3 to 16. However, the examiner respectfully disagrees. Scotto et al. disclose the ratio of fusogen to bulk phospholipid is 0 to 80 mol%, more preferably 1-10 mol% (column 6, lines 4-7). Scotto et al. also disclose an example wherein the ratio of DPPC and DSPC to EPC is 3:7 (Example 3).

4. Applicants also argue on page 16 that Scotto's formulations are not used for incorporating hydrophobic substances. However, Scotto et al. discloses that the fusogen is any lipophilic molecule (column 5, lines 14-18). Therefore, the formulations of Scotto et al. are incorporating a hydrophobic substance, i.e. the fusogen.

5. Applicants argue on pages 16-17 that Castor et al. do not teach that a first and a second phospholipid are required and restricted in the limitation of molar ratio of 3 to 16. However, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejections in view of Castor et al. are also in conjunction with the teachings of Scotto et al. Therefore, the teachings of Scotto et al. are also knowledge of those of ordinary skill in the art.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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